## REMARKS

Applicants submit the present amendment in an effort to advance prosecution and/or to simplify the issues for appeal. The present amendments to the claims do not present any new issues for consideration by the Examiner, in that the amendments merely incorporate subject matter from dependent claims 7 and 53 into the independent claims of the application. In particular, independent claims 1, 17 and 32 are amended to include the subject matter of claims 7 and 53, namely, that the medium contained in the prefilled container contains less than about 3.4 ppm of oxidizable substances after radiation sterilization, and claims 7 and 53 are cancelled. Additionally, the dependencies of dependent claims 52 and 54 are amended, and new dependent claim 56 is added to include similar language as that set forth in pending claims 52 and 54. Accordingly, no new matter has been added. In view of these amendments and the remarks below, entry of this amendment and reconsideration are respectfully requested.

Claims 1-3, 8, 12-13, 16-18, 21-22, 24-25, 28-34, 36-38, 42-43 and 46-51 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Kozimor et al. (U.S. Patent No. 6,231,936; hereinafter "Kozimor"). Additionally, claims 4-5, 23 and 35 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kozimor as applied to claims 1, 2, 17 and 32 and further in view of Jacobs et al (Acta Pharm, IDS; hereinafter "Jacobs"); claims 9, 14-15, 26, 39 and 44-45 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kozimor as applied to claims 8, 25 and 38 and further in view of Williams et al. (U.S. Patent No. 4,994,552; hereinafter "Williams"); claims 10-11, 27 and 40-41 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kozimor as applied to claims 8, 25 and 38 and further in view of Saito

et al. (U.S. Patent No. 6,437,048; hereinafter "Saito"); and claims 19-20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kozimor as applied to claim 18 and further in view of Vellutato (U.S. Patent No. 6,123,900; hereinafter "Vellutato"). As noted above, all of the independent claims 1, 17 and 32 are amended to include the subject matter of claims 7 and 53, which identifies the medium in the container as including less than about 3.4 ppm of oxidizable substances after radiation sterilization. Accordingly, all of these noted rejections are obviated through the above noted amendments. Applicant therefore respectfully requests withdrawal of these rejections.

With respect to the subject matter from claims 7 and 53 which is added to the independent claims, the Office Action also asserts that claims 6-7 and 52-55 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kozimor as applied to claim 1 and further in view of the alleged admitted state of the prior art. In particular, the Office Action alleges that "it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of the Kozimor reference to include limits on UV absorbance value and on hydrogen peroxide value in order to comply with the European and/or US Pharmacopoeia guidelines as taught in the specification." (Office Action at Page 6, Paragraph 6). Applicants respectfully traverse this rejection and request that this rejection be reconsidered and withdrawn for the following reasons.

The present invention as claimed in amended independent claims 1, 17, 32 and 55 is directed to the unexpected and surprising finding that radiation sterilization of a container constructed of polyolefin including a radiation stabilizer will have less of an adverse impact on the contents of the container if the container is prefilled with a medium prior to subjecting the

container to a gamma radiation treatment. Such prefilled containers which have been subjected to a gamma radiation treatment after filling the container with the medium results in the medium exhibiting reduced adverse properties such as a change in pH, change in ultraviolet absorbance, and a change in the amount of oxidizable substances within the medium, when compared with a medium which has been added to a container after the container has been subjected to gamma irradiation. Nothing in the prior art teaches or suggests such unexpected findings.

It is well-known to construct containers useful as medical devices, and particularly syringes, out of polyolefin material. Polyolefin is particularly useful in such applications due to its ease of manufacture and inexpensive raw materials. However, polyolefin materials such as polypropylene are not very stable when subjected to ionizing radiation treatments, particularly gamma irradiation. The present invention provides the unexpected finding that the integrity of a medium contained within the container can be maintained, with the level of oxidizable substances within the medium maintained below about 3.4 ppm, by using radiation stable polyolefins in combination with gamma irradiation, and by ensuring that the container is prefilled with the medium prior to such gamma irradiation treatment.

In particular, the present inventors have discovered that a synergy exists between the composition of the container, the type of sterilization treatment, such as gamma irradiation, and the requirement that a medium being present within the container prior to gamma irradiation. In other words, an adverse reaction of the contents of a prefilled container is inhibited during a radiation sterilization treatment by providing the container as a radiation stable polyolefin material, by prefilling the container with a medium prior to the radiation treatment, and by using gamma radiation for the radiation treatment. Prefilling the container prior to irradiation

minimizes the reactions which incorporate radical scavengers, i.e., oxidizable substances such as hydrogen peroxide, in the container materials by providing a medium to neutralize the radical reactions during irradiation.

Claim 1 specifically recites "[a] method for inhibiting adverse reaction of the contents of a prefilled container during a radiation sterilization procedure", which method involves prefilling the container prior to a gamma sterilization treatment. The prior art fails to teach or even remotely suggest that the contents of a container may be affected based on whether the container is filled or unfilled prior to a radiation treatment.

In particular, Kozimor fails to teach or suggest that prefilling a container with a medium prior to sterilizing the prefilled container with gamma irradiation will result in the unexpected finding that the integrity of the medium is maintained, and thus meets Pharmacopoeia requirements. In fact, the Examiner specifically admits this deficiency in Kozimor, and contends that it would have been obvious to modify Kozimor in order to achieve such a level of oxidizable substances in order to comply with Pharmacopoeia requirements. There is nothing in Kozimor, however, which even remotely suggests that pre-filling the container prior to radiation treatment will achieve such results.

The Office Action contends that Applicants admissions in the specification with respect to the Pharmacopoeia requirements on oxidizable substances provide disclosure which, when combined with Kozimor, render the present invention obvious. This is simply not the case. Applicants' specification merely states what the Pharmacopoeia requirements are. Kozimor does not provide any teachings which would make it obvious for one skilled in the art to reduce sample degradation in an effort to achieve these requirements. Kozimor does not mention or

even allude to any effects whatsoever on the properties of a medium within a container based on whether a radiation treatment occurs before or after the container is filled with the medium. In fact, Kozimor teaches away from the present invention, by discussing that the syringes disclosed in Kozimor can be either prefilled or unfilled prior to irradiation. As demonstrated through the comparative examples in the present application, such is not the case – it is only through prefilling the syringe with a medium and subjecting the prefilled syringe to gamma irradiation that sample degradation is reduced to achieve reduced levels of oxidizable substances within the medium.

For example, Example 3 of the present invention demonstrates the unexpected results seen by the present invention through a comparison of syringes which have been sterilized and then aseptically filled verses those that have been prefilled and then terminally sterilized. In both cases, a radiation stable polyolefin is used as the syringe material, and in both cases the final product is a prefilled syringe. However, as shown through Example 3, testing of the prefilled syringe which was subjected to terminal sterilization in accordance with the method of the present invention demonstrated marked improvement in sample quality when compared to the prefilled syringe which was irradiated and then filled. (Additionally, Example 4 demonstrates that the type of radiation treatment in a terminal sterilization process is important to product quality, in that gamma irradiation reduces the amount of oxidizable materials in a sample as compared with E-beam irradiation.) Kozimor fails in any way to teach or even suggest that the type of radiation treatment used has an effect on the oxidizable substances in the container, or that prefilling the container prior to irradiation has any effect whatsoever on the product sample.

It is only through a hindsight analysis incorporating Applicants' disclosure that such a recognition becomes apparent.

A synergistic effect is realized by the present invention through the specific container material in combination with a specific sterilization treatment with the container filled in a specific manner. The present invention claims a method of inhibiting adverse reaction on the contents of a container by gamma irradiating the container after it is filled, as well as a container treated in such a manner. Kozimor fails to even remotely suggest that the properties of a medium within a container may be affected by whether or not the container is filled before or after the radiation treatment. Contrary to the Examiner's assertion, Applicants discussions as to the Pharmacopoeia requirements do not make up for the clear deficiencies of Kozimor with respect to this lack of teaching. Quite simply, the present inventors have unexpectedly discovered that prefilling a container prior to gamma irradiation will provide an improved product, and nothing in the prior art, whether considered alone or in combination, recognizes this unexpected and surprising result.

In view of these remarks, it is apparent that Kozimor fails to teach, disclose, or suggest that terminal sterilization of a prefilled syringe after it has been filled with a medium inhibits adverse reaction of the medium and maintains the integrity of the medium, with the medium containing less than about 3.4 ppm of oxidizable substances. Accordingly, withdrawal of the rejection based on this reference is respectfully requested.

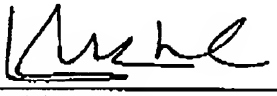
In view of the foregoing amendments and remarks, it is respectfully submitted that all pending claims are now in condition for allowance. Accordingly, entry of this

amendment, reconsideration and withdrawal of the rejection, as well as favorable action are respectfully requested.

Should the Examiner have any questions regarding any of the information contained herein or wish to discuss this matter in further detail, the Examiner is invited to contact Applicants' undersigned representative by telephone at 412-471-8815.

Respectfully submitted,

THE WEBB LAW FIRM

By 

Kirk M. Miles
Registration No. 37,891
Attorney for Applicants
700 Koppers Building
436 Seventh Avenue
Pittsburgh, Pennsylvania 15219
Telephone: 412-471-8815
Facsimile: 412-471-4094
E-mail: webblaw@webblaw.com